Application no.: 10/729,069 Docket no.: SLK-2016-UT

REMARKS

Claim 15 is cancelled herein without prejudice or disclaimer as the Office made final the requirement for restriction between claims of Group I (claims 1-14) and Group II (claims 1-15). Claims 3, 7 and 8 are withdrawn from examination by the Office presumably in view of the species election requirement. Applicants have not cancelled these claims as it is expected they will be examined by the Office upon a finding claims generic to the species are allowable. New claim 21 is added herein and finds basis in the specification, for example, on page 4, paragraph 0012, and pages 14-20, paragraphs 0055-0061. Accordingly, claim 21 adds no prohibitive new matter.

The Office rejected claims 1, 2, 4-6 and 9-14 on a single theory – that the claims allegedly are obvious under 35 U.S.C. §103(a) in view of three documents: Bieniasz, Wigley and Issacs. Claimed matter is *prima facie* obvious only when a combination of cited documents (1) teaches or suggests all of the claimed elements, (2) the person of ordinary skill in the art was motivated to modify the document(s) as suggested in the Office action, and (3) there was a reasonable expectation of success. *See* MPEP 2142, *et seq*. The Applicants respectfully traverse this rejection for the following reasons.

The Cited Combination Does Not Result in the Claimed Subject Matter

Claim 1 is directed to a method for detecting cell fusion in which a first reporter fragment and second reporter fragment, each in different cells, combine to form a functional reporter upon fusion of the cells. Remaining claims 2-14 and 21 depend directly or indirectly upon claim 1.

Bieniasz and Issacs discuss systems in which cell fusion is detected by induction of a reporter gene. In such systems (1) a promoter operatively linked to a reporter gene and (2) an effector of the promoter are in different cells, and upon cell fusion, the effector interacts with the promoter and induces expression of the reporter gene. In Bieniasz the effector is HIV-1 *tat* and the reporter is alkaline phosphatase, and in Issacs the effector is SP6 polymerase and the reporter is luciferase.

The promoter-induced expression assays discussed in Bieniasz and Issacs differ from the claimed methods in the following manners. First, the functional reporter molecule is

generated in the cited documents by transcription and translation after cell fusion. In contrast, the claimed methods do not produce the functional reporter molecule by transcription and translation after cell fusion, but by association of two expressed or existing complementary reporter fragments upon cell fusion. Second, there is no mention in the cited documents of reporter molecule fragments, that can combine to form a functional reporter molecule or incorporating such reporter molecule fragments in different cells prior to fusion, as is in claimed method. Rather, in the cited documents components that assemble after fusion do not directly result in a functional reporter molecule but are components required to transcribe a reporter molecule gene. In addition, the reporter molecule that is eventually formed, by transcription and translation, is made as a single molecule, not fragments that were in different cells prior to fusion.

Wigley discusses a system for detecting and distinguishing soluble folded proteins from mis-folded forms by contacting a free beta-galactosidase omega fragment with a fusion consisting of the target protein and beta-galactosidase alpha fragment. The two beta-galactosidase fragments are expressed within a single bacterial cell. There is no discussion of cell fusion in Wigley, and there is no mention of separating each beta-galactosidase fragment into different cells that are later assembled into a functional reporter molecule upon cell fusion.

Accordingly, the combination of cited documents does not result in the claimed subject matter. Specifically, there is no teaching or suggestion of separating complementary reporter fragments in different cells and allowing them to assemble to form a functional reporter molecule upon cell fusion. The cited combination therefore does not teach or suggest the subject matter of claims 1-14 and 21.

"Obvious to Try" Is An Improper Rationale: There Was No Reasonable Expectation for Success

The Office's modification of Bieniasz and Issacs, by swapping elements of a promoter-induced expression system with complementary reporter fragments discussed in Wigley, is based upon an impermissible "obvious to try" rationale. The Court of Appeals for the Federal Circuit (CAFC) clarified it must be determined whether the prior art, and not Applicants' disclosure, suggested to one of ordinary skill in the art that the claimed process should be carried out and would have a reasonable likelihood of success. *In re Dow Chemical*, 5 USPQ.2d 1529, 1531 (Fed. Cir. 1988).

As described above, the combination of cited documents does not suggest the claimed process should be carried out. There is no teaching in Bieniasz and Issacs that promoter-induced expression of a reporter protein should be or could be replaced with a complementary reporter fragment approach. And there is no teaching in Wigley that complementary reporter fragments could be separated into two cell types for a cell fusion assay system.

There also is no indication that replacing promoter-induced reporter components of Bieniasz and Issacs with complementary reporter fragments would have lead to a functional cell fusion assay. Because Wigley describes only co-expression of beta-galactosidase fragments in one cell, there was no reasonable expectation that each reporter fragment could be split into different cells and successfully utilized in a cell fusion assay until the system was established and tested. The details and successful implementation of the claimed methods are reported in Applicants' present patent application, not in the documents cited.

Thus, the obviousness rejection cannot be founded upon an impermissible "obvious to try" rationale. The pending claims are not obvious because the combination of cited documents provided no suggestion the claimed methods should be carried out and provided no reasonable expectation the claimed methods could be successfully practiced.

There Was No Motivation to Combine the Cited Documents

The CAFC in *In re Rouffet*, 47 USPQ.2d 1453 (Fed. Cir. 1998) reversed a finding of unpatentability by the Board of Appeals on the basis there was no motivation to combine the documents cited for the rejection of Rouffet's claims. The Court identified three possible bases for motivation to combine documents.

The first listed basis, "the nature of the problem to be solved," is not found here as Wigley addressed assays directed to the problem of detecting folded, soluble protein and distinguishing it from mis-folded product. Wigley discussed these methods only in the context of one cell type and not different cells for fusion assays. Thus, there was no motivation to apply the beta-galactosidase fragments discussed in Wigley to cell fusion assays due to differences in the problems to be solved.

The Office alleges Wigley teaches "the diverse application of the system in the study of fundamental biological processes," on page 4 of the Office action. Applicants find Wigley does not provide such a broad teaching. The document pertains only to protein folding/mis-folding assays, and not cell fusion (e.g., first full paragraph on page 135). Thus, Applicants do not understand this

position, and specifically do not understand how assays for detecting protein folding/mis-folding are applicable to cell fusion assays.

The second basis, "the teachings of the prior art," is not found here either as there is no motivation provided by the documents themselves. Bieniasz and Issacs discuss promoter-induced reporter systems and do not mention other reporting methodology, such as the complementary reporting fragments utilized in the claimed methods. Wigley discusses only use of complementary beta-galactosidase fragments, both expressed in a single cell, for assaying protein folding/mis-folding, and does not mention extension of the reporter scheme to different cells for fusion assays. In conclusion, there are no teachings or suggestions in the documents themselves that provide the requisite motivation to combine them.

The third basis is "the knowledge of persons with ordinary skill in the art." In order to apply this basis, the Court stated it would be necessary to "explain what specific understanding or technological principal within the knowledge of one of ordinary skill in the art would have suggested the combination" and concluded that "the Board merely invoked the high level of skill in the field of the art. If such a rote indication would suffice to supply a motivation to combine, the more sophisticated scientific discovery would rarely, if ever, experience a patentable technical advance." The CAFC further commented that the knowledge of persons of ordinary skill in the art may include certain references of special importance (i.e., that one or both of the cited documents is so well know that anyone in the art would be familiar with the documents). An example would be the famous Kholer and Millstein paper on monoclonal antibody preparations.

Here, the Office states it would have been obvious to modify the assay of Bieniasz with features suggested by Issacs and Wigley to "better mimic the actual fusion stage during HIV infection" on page 5 of the Office action. Applicants do not understand the Office's focus on a better mimic of fusion. A fundamental difference between the claimed method and the cited art has nothing to do with cell fusion, but involves the reporting system or readout of the assays. There is no suggestion in the documents themselves that it would be desirable to modify the readout of the assays utilized. Rather, the documents report the assays described therein are functional and no modification is suggested. The Office's statement also does not explain the specific understandings or technological principals that would lead to combining the documents, as required. And the documents cited do not rise to the level of importance that they can be deemed documents of special importance. Thus, there is no showing the level of ordinary skill in the art was sufficient to

combine the cited documents and arrive at the claimed methods.

Thus, the standards for combining documents set forth in *In re Rouffet* are not met by the cited documents.

* * *

In conclusion, (1) the teachings and suggestions of the cited documents in combination do not result in the claimed subject matter, (2) the cited documents in combination provided no reasonable expectation for successfully practicing the claimed methods, and (3) there was no motivation to combine the teachings of the cited documents. The claimed methods therefore are not *prima facie* obvious. Accordingly, it is respectfully requested the Office withdraw the rejection of claims 1, 2, 4-6 and 9-14 under 35 U.S.C. §103(a).

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CONCLUSIONS

Applicants respectfully assert claims 1-14 and 21 are in condition for allowance. Should any issues or questions remain, the Examiner is encouraged to telephone the undersigned at (858) 623-9470 so they may be promptly resolved.

In the unlikely event the transmittal letter is separated from this document and the Office determines that an extension and/or other relief is required, Applicants petition for any required relief, including extensions of time, and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account 503473**.

Respectfully submitted,

Dated: February 6, 2006 By: _____

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